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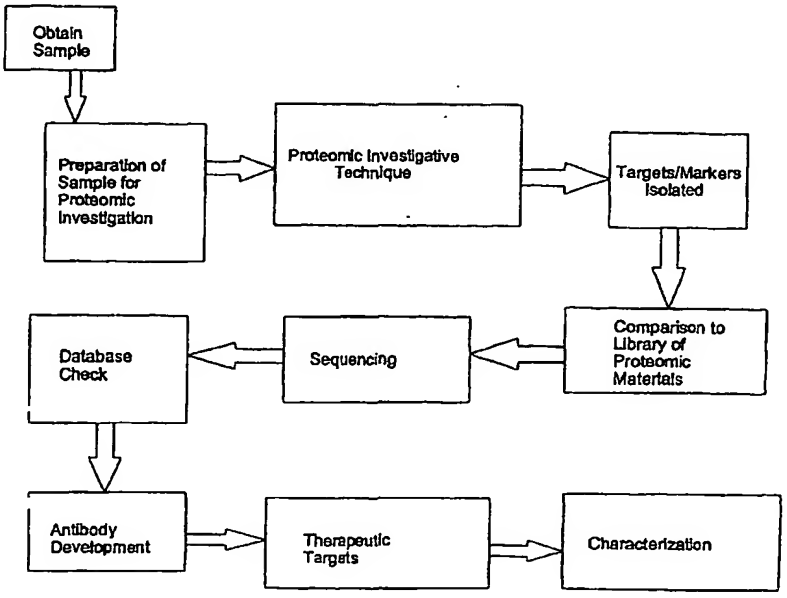
(54) Title: PROCESS FOR DIAGNOSIS OF PHYSIOLOGICAL CONDITIONS BY CHARACTERIZATION OF PROTEOMIC MATERIALS



(57) Abstract: The present invention discloses the use of proteomic investigation as a diagnostic tool; and particularly teaches the use of proteomic investigative techniques and methodology to determine a proteomic basis for the development and progression of abnormal physiological conditions and the development and characterization of risk assessment, diagnostic and therapeutic means and methodologies.

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PROCESS FOR DIAGNOSIS OF PHYSIOLOGICAL CONDITIONS BY CHARACTERIZATION OF PROTEOMIC MATERIALS

FIELD OF THE INVENTION

This invention generally relates to the use of proteomic investigation as a diagnostic tool; and particularly to the use of proteomic investigative techniques and methodology to determine a proteomic basis for the development and progression of abnormal physiological conditions.

BACKGROUND OF THE INVENTION

At the present time there exist numerous diagnostic techniques and procedures whose goal is to assess an individual's physiological condition. From a very early age, individuals are subjected to a variety of routine physical examinations with the goal of maintaining a vibrant and healthful existence. During the course of these examinations, a physician will often require a variety of diagnostic procedures based upon several factors, for example the patient's physical presentation, familial history, environmental factors which may place the patient at particular risk, and tests to ascertain or predict the course or progress of known conditions.

Routine tests generally include blood and urine analysis and X-rays, and often include electrocardiogram (EKG), cardiac stress tests and the like. Dependent upon preliminary findings, additional tests may be ordered, in accordance with current standards of care, and may include computer assisted tomography (CAT) scans, magnetic resonance imagery (MRI), echocardiographic studies, Doppler analysis, angiograms, elctromyograph (EMG), electroencephelograph (EEG), and the like procedures which are geared to assist the physician in forming a definitive diagnosis. The majority of these tests are directed toward quantifying a particular condition, usually during a point of exacerbation of the condition.

Unfortunately, even the most skilled diagnostician may not always be able to successfully determine the reasons for a particular clinical condition or the underlying cause of the manifestation of certain symptoms. Thus, conditions are often misdiagnosed, and medications are often ordered which are inappropriate or ineffective. Furthermore, very few tests exist which offer the diagnostician a prospective method of

analyzing the propensity for an individual to develop a particular condition.

As we delve more deeply into our genetic makeup, we are becoming increasingly aware of genetic anomalies which cause us to be particularly inclined to either develop or manifest a wide variety of conditions. The genetic information of all living organisms (e.g. animals, plants and microorganisms) is encoded in deoxyribonucleic acid (DNA). In humans, the complete genome is now believed to be comprised of about 30,000 - 40,000 genes located on 24 chromosomes.

While each of these genes, or nucleotide sequences, encodes a single protein, or several splice variants (approximately 10 or more) these may be post-translationally modified into many different forms having different molecular masses. Subsequent to their expression via transcription, translation, and post-translational modification, each protein or fragment thereof is capable of fulfilling a specific biochemical function within a living cell.

Changes in a DNA sequence are known as mutations and can result in proteins with altered or in some cases even lost biochemical activities; this in turn can cause genetic disease. Such mutations may include nucleotide deletions, insertions or alterations (i.e. point mutations). Point mutations can be either "missense", resulting in a change in the amino acid sequence of a protein or "nonsense" coding for a stop codon and thereby leading to a truncated protein.

It is currently believed that there are more than 3000 genetically related diseases including hemophilias, thalassemias, Duchenne Muscular Dystrophy (DMD), Huntington's Disease (HD), Alzheimer's Disease and Cystic Fibrosis (CF). In addition to mutated genes, which result in genetic disease, certain birth defects are the result of chromosomal abnormalities such as Trisomy 21 (Down's Syndrome), Trisomy 13 (Patau Syndrome), Trisomy 18 (Edward's Syndrome), Monosomy X (Turner's Syndrome) and other sex chromosome aneuploidies such as Klienfelter's Syndrome (XXY). Further, there is growing evidence that certain DNA sequences may predispose an individual to any of a number of diseases such as diabetes, arteriosclerosis, obesity, various autoimmune diseases and cancer (e.g. colorectal, breast,ovarian, lung).

The science of proteomics recognizes that messenger RNAs, which are transcripts of genomic DNA that directly encode proteins, are assemblable in a variety

of ways, and that expressed proteins can further be modified, e.g. by methods such as phosphorylation and glycosylation leading to variations in protein expression.

As broadly defined, leading experts in the field of proteomics describe the science as including transcriptional profiling to determine those genes which are transcribed into RNA in a particular cell type, developmental stage or disease state. The science seeks to provide methods and techniques for high-throughput expression and purification of proteins. Additionally, the science of proteomics seeks to study protein profiling by the use of various techniques, so-called proteomic investigative techniques, including two-dimensional gel electrophoresis and mass spectroscopy, co-immunoprecipation, affinity chromatography, protein binding analysis, overlay analysis and BIACORE, use of the yeast two-hybrid method for studies of protein-protein interaction, pathway analysis for interpreting signal transduction and complex cellular processes, three-dimensional structure studies and large-scale protein folding, and the use of bioinformatics analysis of proteomics data.

Various techniques have been put forth for analyzing the protein constituents of either whole cells or of cell organelles. By separating proteins in a first dimension based upon charge and in a second dimension based upon molecular size, individual proteins on the gel can be isolated and characterized. The drawback of this technique is that the gels are difficult to analyze, their resolving power often being insufficient to separate the various distinct proteins present in a particular sample. Furthermore, there is a distinct lack of reproducibility from one gel sample to the next and the paucity of reproducible data along with the similarity of data between different tissues, species and organism states makes the development of bioinformatics databases problematic. Although there have been advances in software techniques to bring greater degrees of standardization and reproducibility to 2D-gel analysis, significant obstacles remain.

There is ongoing research in the field of protein expression profiling using 2D-gel in conjunction with other techniques. Using laser capture microdissection, researchers obtain both diseased and normal cells. Using 2D-gel analysis, all the protein components in these cells are separated and capillary high performance liquid chromatography (HPLC) or electrospray ion-trap mass spectroscopy are utilized to identify differing levels of protein expression in diseased versus normal cells.

An additional technique in proteomics is the use of phage display, wherein peptide or protein libraries are created on viral surfaces and are then screened on a mass scale. Since the proteins remain with their encoding genes, identification is facilitated. This is more valuable as a genomics tool than a proteomics tool since differential expression is still not usefully elucidated. A similar technique called profusion forms molecules which are conjugates in which a peptide or protein is chemically linked to its encoding mRNA, therefore facilitating affinity screening techniques. In addition, techniques exist for identifying antibody fragments which bind human proteins. Detection is simplified by tagging each antibody fragment with a peptide encoding sequence. Subsequent testing of tissue samples for the presence of corresponding target proteins can then be studied so as to determine their relevance as possible therapeutic or diagnostic agents.

Methods utilizing mass spectrometry for the analysis of a target polypeptide have been taught wherein the polypeptide is first solubilized in an appropriate solution or reagent system. The type of solution or reagent system, e.g., comprising an organic or inorganic solvent, will depend on the properties of the polypeptide and the type of mass spectrometry performed and are well known in the art (see, e.g., Vorm et al. (1994) Anal. Chem. 66:3281 (for MALDI) and Valaskovic et al. (1995) Anal. Chem. 67:3802 (for ESI). Mass spectrometry of peptides is further disclosed, e.g., in WO 93/24834 by Chait et al.

In one prior art embodiment, the solvent is chosen so that the risk that the molecules may be decomposed by the energy introduced for the vaporization process is considerably reduced, or even fully excluded. This can be achieved by embedding the sample in a matrix, which can be an organic compound, e.g., sugar, in particular pentose or hexose, but also polysaccharides such as cellulose. These compounds are decomposed thermolytically into CO_2 and H_2O so that no residues are formed which might lead to chemical reactions. The matrix can also be an inorganic compound, e.g., nitrate of ammonium which is decomposed practically without leaving any residues. Use of these and other solvents are further disclosed in U.S. Pat. No. 5,062,935 by Schlag et al.

Prior art mass spectrometer formats for use in analyzing the translation products

include ionization (I) techniques, including but not limited to matrix assisted laser desorption (MALDI), continuous or pulsed electrospray (ESI) and related methods (e.g., IONSPRAY or THERMOSPRAY), or massive cluster impact (MCI); these ion sources can be matched with detection formats including linear or non-linear reflection time-of-flight (TOF), single or multiple quadropole, single or multiple magnetic sector, Fourier Transform ion cyclotron resonance (FTICR), ion trap, and combinations thereof (e.g., ion-trap/time-of-flight). For ionization, numerous matrix/wavelength combinations (MALDI) or solvent combinations (ESI) can be employed. Subattomole levels of protein have been detected, for example, using ESI (Valaskovic, G. A. et al., (1996) Science 273:1199-1202) or MALDI (Li, L. et al., (1996) J. Am. Chem. Soc. 118:1662-1663) mass spectrometry.

ES mass spectrometry has been introduced by Fenn et al. (J. Phys. Chem. 88, 4451-59 (1984); PCT Application No. WO 90/14148) and current applications are summarized in recent review articles (R. D. Smith et al., Anal. Chem. 62, 882-89 (1990) and B. Ardrey, Electrospray Mass Spectrometry, *Spectroscopy* Europe, 4, 10-18 (1992)). MALDI-TOF mass spectrometry has been introduced by Hillenkamp et al. ("Matrix Assisted UV-Laser Desorption/Ionization: A New Approach to Mass Spectrometry of Large Biomolecules," Biological Mass Spectrometry (Burlingame and McCloskey, editors), Elsevier Science Publishers, Amsterdam, pp. 49-60, 1990). With ESI, the determination of molecular weights in femtomole amounts of sample is very accurate due to the presence of multiple ion peaks which all could be used for the mass calculation.

The mass of the target polypeptide determined by mass spectrometry is then compared to the mass of a reference polypeptide of known identity. In one embodiment, the target polypeptide is a polypeptide containing a number of repeated amino acids directly correlated to the number of trinucleotide repeats transcribed/translated from DNA; from its mass alone the number of repeated trinucleotide repeats in the original DNA which coded it, may be deduced.

U.S. Patent No. 6,020,208 utilizes a general category of probe elements (i.e., sample presenting means) with Surfaces Enhanced for Laser Desorption/Ionization (SELDI), within which there are three (3) separate subcategories. The SELDI process is

directed toward a sample presenting means (i.e., probe element surface) with surface-associated (or surface-bound) molecules to promote the attachment (tethering or anchoring) and subsequent detachment of tethered analyte molecules in a light-dependent manner, wherein the said surface molecule(s) are selected from the group consisting of photoactive (photolabile) molecules that participate in the binding (docking, tethering, or crosslinking) of the analyte molecules to the sample presenting means (by covalent attachment mechanisms or otherwise).

PCT/EP/04396 teaches a process for determining the status of an organism by peptide measurement. The reference teaches the measurement of peptides in a sample of the organism which contains both high and low molecular weight peptides and acts as an indicator of the organism's status. The reference concentrates on the measurement of low molecular weight peptides, i.e. below 30,000 Daltons, whose distribution serves as a representative cross-section of defined controls. Contrary to the methodology of the instant invention, the '396 patent strives to determine the status of a healthy organism, i.e. a "normal" and then use this as a reference to differentiate disease states. The present inventors do not attempt to develop a reference "normal", but rather strive to specify particular markers which are evidentiary of at least one specific disease state, whereby the presence of said marker serves as a positive indicator of disease. This leads to a simple method of analysis which can easily be performed by an untrained individual, since there is a positive correlation of data. On the contrary, the '396 patent requires a complicated analysis by a highly trained individual to determine disease state versus the perception of non-disease or normal physiology.

Richter et al, Journal of Chromatography B, 726(1999) 25-35, refer to a database established from human hemofiltrate comprised of a mass database and a sequence database. The goal of Richter et al was to analyze the composition of the peptide fraction in human blood. Using MALDI-TOF, over 20,000 molecular masses were detected representing an estimated 5,000 different peptides. The conclusion of the study was that the hemofiltrate (HF) represented the peptide composition of plasma. No correlation of peptides with relation to normal and/or disease states is made.

As used herein, "analyte" refers to any atom and/or molecule; including their complexes and fragment ions. In the case of biological molecules/macromolecules or

"biopolymers", such analytes include but are not limited to: proteins, peptides, DNA, RNA, carbohydrates, steroids, and lipids. Note that most important biomolecules under investigation for their involvement in the structure or regulation of life processes are quite large (typically several thousand times larger than H_2O.

As used herein, the term "molecular ions" refers to molecules in the charged or ionized state, typically by the addition or loss of one or more protons (H^+).

As used herein, the term "molecular fragmentation" or "fragment ions" refers to breakdown products of analyte molecules caused, for example, during laser-induced desorption (especially in the absence of added matrix).

As used herein, the term "solid phase" refers to the condition of being in the solid state, for example, on the probe element surface.

As used herein, "gas" or "vapor phase" refers to molecules in the gaseous state (i.e., in vacuo for mass spectrometry).

As used herein, the term "analyte desorption/ionization" refers to the transition of analytes from the solid phase to the gas phase as ions. Note that the successful desorption/ionization of large, intact molecular ions by laser desorption is relatively recent (circa 1988)--the big breakthrough was the chance discovery of an appropriate matrix (nicotinic acid).

As used herein, the term "gas phase molecular ions" refers to those ions that enter into the gas phase. Note that large molecular mass ions such as proteins (typical mass=60,000 to 70,000 times the mass of a single proton) are typically not volatile (i.e., they do not normally enter into the gas or vapor phase). However, in the procedure of the present invention, large molecular mass ions such as proteins do enter the gas or vapor phase.

As used herein in the case of MALDI, the term "matrix" refers to any one of several small, acidic, light absorbing chemicals (e.g., nicotinic or sinapinic acid) that is mixed in solution with the analyte in such a manner so that, upon drying on the probe element, the crystalline matrix-embedded analyte molecules are successfully desorbed (by laser irradiation) and ionized from the solid phase (crystals) into the gaseous or vapor phase and accelerated as intact molecular ions. For the MALDI process to be successful, analyte is mixed with a freshly prepared solution of the chemical matrix

(e.g., 10,000:1 matrix:analyte) and placed on the inert probe element surface to air dry just before the mass spectrometric analysis. The large fold molar excess of matrix, present at concentrations near saturation, facilitates crystal formation and entrapment of analyte.

As used herein, "energy absorbing molecules (EAM)" refers to any one of several small, light absorbing chemicals that, when presented on the surface of a probe, facilitate the neat desorption of molecules from the solid phase (i.e., surface) into the gaseous or vapor phase for subsequent acceleration as intact molecular ions. The term EAM is preferred, especially in reference to SELDI. Note that analyte desorption by the SELDI process is defined as a surface-dependent process (i.e., neat analyte is placed on a surface composed of bound EAM). In contrast, MALDI is presently thought to facilitate analyte desorption by a volcanic eruption-type process that "throws" the entire surface into the gas phase. Furthermore, note that some EAM when used as free chemicals to embed analyte molecules as described for the MALDI process will not work (i.e., they do not promote molecular desorption, thus they are not suitable matrix molecules).

As used herein, "probe element" or "sample presenting device" refers to an element having the following properties: it is inert (for example, typically stainless steel) and active (probe elements with surfaces enhanced to contain EAM and/or molecular capture devices).

As used herein, "MALDI" refers to Matrix-Assisted Laser Desorption/Ionization As used herein, "TOF" stands for Time-of-Flight.

As used herein, "MS" refers to Mass Spectrometry.

As used herein "MALDI-TOF MS" refers to Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry.

As used herein, "ESI" is an abbreviation for Electrospray ionization.

As used herein, "chemical bonds" is used simply as an attempt to distinguish a rational, deliberate, and knowledgeable manipulation of known classes of chemical interactions from the poorly defined kind of general adherence observed when one chemical substance (e.g., matrix) is placed on another substance (e.g., an inert probe element surface). Types of defined chemical bonds include electrostatic or ionic (+/-)

bonds (e.g., between a positively and negatively charged groups on a protein surface), covalent bonds (very strong or "permanent" bonds resulting from true electron sharing), coordinate covalent bonds (e.g., between electron donor groups in proteins and transition metal ions such as copper or iron), and hydrophobic interactions (such as between two noncharged groups).

As used herein, "electron donor groups" refers to the case of biochemistry, where atoms in biomolecules (e.g, N, S, O) "donate" or share electrons with electron poor groups (e.g., Cu ions and other transition metal ions).

With the advent of mass spectroscopic methods such as MALDI and SELDI, researchers have begun to utilize a tool that holds the promise of uncovering countless biopolymers which result from translation, transcription and post-translational transcription of proteins from the entire genome.

Operating upon the principles of retentate chromatography, SELDI MS involves the adsorption of proteins, based upon their physico-chemical properties at a given pH and salt concentration, followed by selectively desorbing proteins from the surface by varying pH, salt, or organic solvent concentration. After selective desorption, the proteins retained on the SELDI surface, the "chip", can be analyzed using the CIPHERGEN protein detection system, or an equivalent thereof. Retentate chromatography is limited, however, by the fact that if unfractionated body fluids, e.g. blood, blood products, urine, saliva, and the like, along with tissue samples, are applied to the adsorbent surfaces, the biopolymers present in the greatest abundance will compete for all the available binding sites and thereby prevent or preclude less abundant biopolymers from interacting with them, thereby reducing or eliminating the diversity of biopolymers which are readily ascertainable.

If a process could be devised for maximizing the diversity of biopolymers discernable from a sample, the ability of researchers to accurately determine the relevance of such biopolymers with relation to one or more disease states would be immeasurably enhanced. Such determinations would then lead to the production of protein expression profiles. These profiles or phenomic fingerprints may be used to simultaneously monitor multiple protein markers associated with differing biological states.

What is therefore lacking in the art is a rapid process for separation of proteomics materials, which are variously defined as an "analyte" referring to any atom and/or molecule; including their complexes and fragment ions; or in the case of biological molecules/macromolecules or "biopolymers", wherein such materials include but are not limited to: proteins, peptides, DNA, RNA, carbohydrates, steroids, and lipids, polypeptides, peptide fragments, modified proteins, non-limiting examples of which are glycoproteins, lipoproteins and the like, and related cellular and sub-cellular components. Additionally lacking is a method for identification of their function as it relates to either a normal or an abnormal physiological state, and a method for comparing the presence or absence of particular proteomic materials or groupings thereof, in living cells, which would be indicative or predictive of the presence or predicted development of an abnormal physiological condition or state.

DESCRIPTION OF THE PRIOR ART

United States Patent 5,010,175 discloses a method for producing and selecting peptides with specific properties comprising obtaining selected individual peptides or families thereof which have a target property and optionally determining the amino acid sequence of a selected peptide or peptides to permit synthesis in practical quantities.

United States Patent 5,538,897 teaches a method for correlating a peptide fragment mass spectrum with amino acid sequences derived from a database. A peptide is analyzed by a tandem mass spectrometer to yield a peptide fragment mass spectrum. A protein sequence database or a nucleotide sequence database is used to predict one or more fragment spectra for comparison with the experimentally derived fragment spectrum. In one embodiment, sub-sequences of the sequences found on the database which define a peptide having a mass substantially equal to the mass of the peptide analyzed by the tandem mass spectrometer are identified as candidate sequences. For each candidate sequence, a plurality of fragments of the sequence are identified and the masses and m/z ratios of the fragments are predicted and used to form a predicted mass spectrum. The various predicted mass spectra are compared to the experimentally derived fragment spectrum using a closeness-of-fit measure, preferably calculated with a two-step process, including a calculation of a preliminary score and, for the

highest-scoring predicted spectra, calculation of a correlation function. While useful to determine the source of a particular fragment, the method fails to teach or suggest a means for diagnosing a physiological condition by characterization of proteomic materials.

U.S.Patent 5,808,300 teaches that MALDI MS has been used to generate images of samples in one or more pictures, providing the capability of mapping concentrations of specific molecules in X,Y coordinates of the original sample. For sections of mammalian tissue, for example, this can be accomplished in two ways. First, tissue slices can be directly analyzed after thorough drying and application of a thin coating of matrix by electrospray. Second, imprints of the tissue can be analyzed by blotting the dry tissue sections on specially prepared targets, e.g., C-18 beads. Peptides and small proteins bind to the C-18 and create a positive imprint of the tissue which can be imaged by MALDI MS after application of matrix. Such images can be displayed in individual m/z values as a selected ion image which would localize individual compounds in the tissue, as summed ion images, or as a total ion image which would be analogous to a photomicrograph. This imaging process may also be applied to separation techniques where a physical track or other X,Y deposition process is utilized, for example, in the CE/MALDI MS combination where a track is deposited on a membrane target.

U.S. Patent 6,043,031 provides fast and highly accurate mass spectrometer based processes for detecting a particular nucleic acid sequence in a biological sample. Depending on the sequence to be detected, the processes can be used, for example, to diagnose a genetic disease or chromosomal abnormality; a predisposition to a disease or condition, infection by a pathogenic organism, or for determining identity or heredity.

U. S. Patent 6,189,013 discloses a project-based full length biomolecular sequence database which is a relational database system for storing biomolecular sequence information in a manner that allows sequences to be catalogued and searched according to association with one or more projects for obtaining full-length biomolecular sequences from shorter sequences. The relational database has sequence records containing information identifying one or more projects to

which each of the sequence records belong. Each project groups together one or more biomolecular sequences generated during work to obtain a full-length gene sequence from a shorter sequence. The computer system has a user interface allowing a user to selectively view information regarding one or more projects. The relational database also provides interfaces and methods for accessing and manipulating and analyzing project-based information.

SUMMARY OF THE INVENTION

The instantly disclosed invention is drawn to a process for determining a proteomic basis, e.g. a basis for diagnosing the existence of or predicting the development and/or progression of abnormal physiological conditions based upon the presence of proteomic materials, by first obtaining a patient sample containing such proteomic material(s); preparing said patient sample to facilitate proteomic investigation thereof; isolating one or more patient specific proteomic materials from said patient sample; and comparing said one or more isolated patient specific proteomic materials against a library of proteomic materials having characteristics identifiable with both normal and abnormal physiological conditions or predictive hallmarks thereof. The proteomic materials may be separated into desired sets of diverse moieties by the use of one or more preparations steps. This process permits analysis of one or more of these isolated patient specific proteomic materials thereby enabling the diagnostician to ultimately characterize an individual's condition as being either positively or negatively indicative of one or more abnormal physiological conditions or predictive hallmarks thereof.

Also disclosed is a process for sequencing said one or more isolated patient specific proteomic materials, wherein the particular peptide/polypeptide, proteins, nucleotide or oligonucleotide, or the like proteomic material associated therewith is identified. This information permits the development of quantifiable data-linking methodologies upon the appreciation of particular proteomic materials with particular physiological abnormalities.

As a useful diagnostic tool, the process of the invention further includes the step of developing at least one antibody to said isolated patient specific proteomic material

and may subsequently express at least one protein marker specific to said at least one antibody to said isolated patient specific proteomic material.

As a means of determining the significance of an isolated proteomic material, the process may include at least one interactive mapping step to characterize said material. The interactive mapping step may include one or more steps selected from the group consisting of creation of engineered antibodies or proteins, directly determining the three-dimensional structure of said antibody or protein directly from an amino acid sequence thereof; cellular localization, sub-cellular localization, protein-protein interaction, receptor-ligand interaction, and pathway delineation. Included in such mapping techniques may be co-immunoprecipitation, protein or antibody affinity chromatography, protein binding analysis including BIACORE, U.V. spectra, overlay analysis, far Western analysis, immuno-metric analysis, and ELISA. As referred to in this disclosure, engineered antibodies or proteins include, but are not limited to, those which are tagged with a material selected from the group consisting of GFP, colloidal gold, streptavidin, avidin and biotin. Proteomic materials are illustrated by, but not limited to, proteins, peptides or fragments thereof and related isomers and retro-isomers, e.g. an immunologically reactive/detectable fragment thereof, glycoproteins, lipoproteins, modified proteins and the like, antibodies and protein marker.

Accordingly, it is an objective of the instant invention to teach methods for proteomic investigation.

It is another objective of the instant invention to define a particularly isolated proteomic material which is useful in evidencing and categorizing at least one particular physiological condition or predictive hallmark thereof.

It is another objective of the instant invention to evaluate samples containing a plurality of analytes/biopolymers for the presence of physiological condition specific sequences.

It is a further objective of the instant invention to elucidate essentially all biopolymeric moieties contained therein, whereby particularly significant moieties may be identified.

It is a further objective of the instant invention to provide at least one purified antibody which is specific to said particularly isolated proteomic material.

It is yet another objective of the instant invention to teach a monoclonal antibody which is specific to said particularly isolated proteomic material.

It is a still further objective of the invention to teach polyclonal antibodies raised against said particularly isolated proteomic material.

It is yet an additional objective of the instant invention to teach a diagnostic kit for determining the presence of said particularly isolated proteomic material.

It is a still further objective of the instant invention to teach methods for characterizing disease state based upon the identification of said particularly isolated proteomic material.

Other objects and advantages of this invention will become apparent from the following description taken in conjunction with the accompanying drawings wherein are set forth, by way of illustration and example, certain embodiments of this invention. The drawings constitute a part of this specification and include exemplary embodiments of the present invention and illustrate various objects and features thereof.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a block diagram illustrating the proteomic investigative process.

DETAILED DESCRIPTION OF THE INVENTION

Serum samples from individuals were analyzed using Surface Enhanced Laser Desorption Ionization (SELDI) as a proteomic investigative technique using the Ciphergen PROTEINCHIP system. The chip surfaces included, but were not limited to IMAC-3-Ni, SAX2 surface chemistries, gold chips, and the like.

Preparatory to the conduction of the SELDI MS procedure, various preparatory steps were carried out in order to maximize the diversity of discernible moities educable from the sample.

Utilizing a type of micro-chromatographic column called a C18- ZIPTIP available from the Millipore company, the following preparatory steps were conducted.

1. Dilute sera in sample buffer
2. Aspirate and dispense ZIP TIP in 50% Acetonitrile
3. Aspirate and dispense ZIP TIP in Equilibration solution

4. Aspirate and Dispense in serum sample
5. Aspirate and Dispense ZIP TIP in Wash solution
6. Aspirate and Dispense ZIP TIP in Elution Solution

Illustrative of the various buffering compositions useful in the present invention are:

Sample Buffers (various low pH's): Hydrochloric acid (HCl), Formic acid, Trifluoroacetic acid (TFA),

Equilibration Buffers (various low pH's): HCl, Formic acid, TFA;

Wash Buffers (various low pH's): HCl, Formic acid, TFA;

Elution Solutions (various low pH's and % Solvents):

HCl, Formic acid, TFA;

Solvents: Ethanol,Methanol, Acetonitrile.

Spotting was then performed, for example upon a Gold Chip in the following manner:

1. spot 2 ul of sample onto each spot
2. let sample partially dry
3. spot 1 ul of matrx, and let air dry.

HiQ Anion Exchange Mini Column Protocol

1. Dilute sera in sample/running buffer;
2. Add HiQ resin to column and remove any air bubbles;
3. Add Uf water to aid in column packing;
4. Add sample/running buffer to equilibrate column;
5. Add diluted sera;
6. Collect all the flow through fraction in Eppendorf tubes until level is at resin;
7. Add sample/running buffer to wash column;
8. Add elusion buffer and collect elusion in Eppendorf tubes.

Illustrative of the various buffering compositions useful in this technique are:

Sample/Running buffers: including but not limited to Bicine buffers of various molarities, pH's, NaCl content, Bis-Tris buffers of various molarities, pH's, NaCl content, Diethanolamine of various molarities, pH's, NaCl content, Diethylamine of various molarities, pH's, NaCl content, Imidazole of various molarities, pH's, NaCl

content, Tricine of various molarities, pH's, NaCl content, Triethanolamine of various molarities, pH's, NaCl content, Tris of various molarities, pH's, NaCl content.

Elution Buffer: Acetic acid of various molarities, pH's, NaCl content, Citric acid of various molarities, pH's, NaCl content, HEPES of various molarities, pH's, NaCl content, MES of various molarities, pH's, NaCl content, MOPS of various molarities, pH's, NaCl content, PIPES of various molarities, pH's, NaCl content, Lactic acid of various molarities, pH's, NaCl content, Phosphate of various molarities, pH's, NaCl content, Tricine of various molarities, pH's, NaCl content.

Chelating Sepharose Mini Column

1. Dilute Sera in Sample/Running buffer;
2. Add Chelating Sepharose slurry to column and allow column to pack;
3. Add UF water to the column to aid in packing;
4. Add Charging Buffer once water is at the level of the resin surface;
5. Add UF water to wash through non bound metal ions once charge buffer washes through;
6. Add running buffer to equilibrate column for sample loading;
7. Add diluted serum sample;
8. Add running buffer to wash unbound protein;
9. Add elution buffer and collect elution fractions for analysis;
10. Acidify each elution fraction.

Illustrative of the various buffering compositions useful in this technique are:

Sample/Running buffers including but not limited to Sodium Phosphate buffers at various molarities and pH's;

Charging buffers including but not limited to Nickel Chloride, Nickel Sulphate, Copper II Chloride, Zinc Chloride or any suitable metal ion solution;

Elution Buffers including but not limited to Sodium phosphate buffers at various molarities and pH's containing various molarities of EDTA and/or Imidazole.

HiS Cation Exchange Mini Column Protocol

1. Dilute sera in sample/running buffer;
2. Add HiS resin to column and remove any air bubbles;
3. Add Uf water to aid in column packing;

4. Add sample/running buffer to equilibrate column for sample loading;

5. Add diluted sera to column;

6. Collect all flow through fractions in Eppendorf tubes until level is at resin.

7. Add sample/running buffer to wash column.

8. Add elusion buffer and collect elusion in Eppendorf tubes.

Illustrative of the various buffering compositions useful in this technique are:

Sample/Running buffers: including but not limited to Bicine buffers of various molarities, pH's, NaCl content, Bis-Tris buffers of various molarities, pH's, NaCl content, Diethanolamine of various molarities, pH's, NaCl content, Diethylamine of various molarities, pH's, NaCl content, Imidazole of various molarities, pH's, NaCl content, Tricine of various molarities, pH's, NaCl content, Triethanolamine of various molarities, pH's, NaCl content, Tris of various molarities, pH's, NaCl content.

Elution Buffer: Acetic acid of various molarities, pH's, NaCl content, Citric acid of various molarities, pH's, NaCl content, HEPES of various molarities, pH's, NaCl content, MES of various molarities, pH's, NaCl content, MOPS of various molarities, pH's, NaCl content, PIPES of various molarities, pH's, NaCl content, Lactic acid of various molarities, pH's, NaCl content, Phosphate of various molarities, pH's, NaCl content, Tricine of various molarities, pH's, NaCl content.

The procedure for profiling serum samples is described below:

Following the preparatory steps illustrated above, various methods for use of the PROTEINCHIP arrays, available for purchase from Ciphergen Biosystems (Palo Alto, CA), may be practiced. Illustrative of one such method is as follows.

The first step involved treatment of each spot with 20 ml of a solution of 0.5 M EDTA for 5 minutes at room temperature in order to remove any contaminating divalent metal ions from the surface. This was followed by rinsing under a stream of ultra-filtered, deionized water to remove the EDTA. The rinsed surfaces were treated with 20 ml of 100 mM Nickel sulfate solution for 5 minutes at room temperature after which the surface was rinsed under a stream of ultra-filtered, deionized water and allowed to air dry.

Serum samples (2 ml) were applied to each spot (now "charged" with the metal-Nickel) and the PROTEINCHIP was returned to the plastic container in which it was supplied.

A piece of moist KIMWIPE was placed at the bottom of the container to generate a humid atmosphere. The cap on the plastic tube was replaced and the chip allowed to incubate at room temperature for one hour. At the end of the incubation period, the chip was removed from the humid container and washed under a stream of ultra-filtered, deionized water and allowed to air dry. The chip surfaces (spots) were now treated with an energy-absorbing molecule that helps in the ionization of the proteins adhering to the spots for analysis by Mass Spectrometry. The energy-absorbing molecule in this case was sinapinic acid and a saturated solution prepared in 50% acetonitrile and 0.05% TFA was applied (1 ml) to each spot. The solution was allowed to air dry and the chip analyzed immediately using MS (SELDI).

Serum samples from patients suffering from a variety of disease states were analyzed using one or more protein chip surfaces, e.g. a gold chip or an IMAC nickel chip surface as described above and the profiles were analyzed to discern notable sequences which were deemed in some way evidentiary of at least physiological condition or disease state.

Patient specific samples were obtained and the data used to formulate a library of proteomic materials having characteristics identifiable with both normal and abnormal physiological conditions or predictive hallmarks thereof. Data which is exemplary of the information retrieved via the novel proteomic investigative techniques of the instant invention is set forth in Appendix A.

Although all manner of biomarkers related to all disease conditions are deemed to be within the purview of the instant invention and methodology, particular significance was given to those markers and diseases associated with the complement system and Syndrome X and diseases related thereto.

The complement system is an important part of non-clonal or innate immunity that collaborates with acquired immunity to destroy invading pathogens and to facilitate the clearance of immune complexes from the system. This system is the major effector of the humoral branch of the immune system, consisting of nearly 30 serum and membrane proteins. The proteins and glycoproteins composing the complement system are synthesized largely by liver hepatocytes. Activation of the complement system involves a sequential enzyme cascade in which the proenzyme product of one step

becomes the enzyme catalyst of the next step. Complement activation can occur via two pathways: the classical and the alternative. The classical pathway is commonly initiated by the formation of soluble antigen-antibody complexes or by the binding of antibody to antigen on a suitable target, such as a bacterial cell. The alternative pathway is generally initiated by various cell-surface constituents that are foreign to the host. Each complement component is designated by numerals (C1-C9), by letter symbols, or by trivial names. After a component is activated, the peptide fragments are denoted by small letters. The complement fragments interact with one another to form functional complexes. Ultimately, foreign cells are destroyed through the process of a membrane-attack complex mediated lysis.

The C4 component of the complement system is involved in the classical activation pathway. It is a glycoprotein containing three polypeptide chains (α, β, and γ). C4 is a substrate of component C1s and is activated when C1s hydrolyzes a small fragment (C4a) from the amino terminus of the α chain, exposing a binding site on the larger fragment (C4b).

The native C3 component consists of two polypeptide chains, α and β. As a serum protein, C3 is involved in the alternative pathway. Serum C3, which contains an unstable thioester bond, is subject to slow spontaneous hydrolysis into C3a and C3b. The C3f component is involved in the regulation required of the complement system which confines the reaction to designated targets. During the regulation process, C3b is cleaved into two parts: C3bi and C3f. C3bi is a membrane-bound intermediate wherein C3f is a free diffusible (soluble) component.

Complement components have been implicated in the pathogenesis of several disease conditions. C3 deficiencies have the most severe clinical manifestations, such as recurrent bacterial infections and immune-complex diseases, reflecting the central role of C3. The rapid profusion of C3f moieties and resultant "accidental" lysis of normal cells mediated thereby gives rise to a host of auto-immune reactions. The ability to understand and control these mechanisms, along with their attendant consequences, will enable practitioners to develop both diagnostic and therapeutic avenues by which to thwart these maladies.

In the course of defining a plurality of disease specific marker sequences, special significance was given to markers which were evidentiary of a particular disease state or with conditions associated with Syndrome-X. Syndrome-X is a multifaceted syndrome, which occurs frequently in the general population. A large segment of the adult population of industrialized countries develops this metabolic syndrome, produced by genetic, hormonal and lifestyle factors such as obesity, physical inactivity and certain nutrient excesses. This disease is characterized by the clustering of insulin resistance and hyperinsulinemia, and is often associated with dyslipidemia (atherogenic plasma lipid profile), essential hypertension, abdominal (visceral) obesity, glucose intolerance or noninsulin-dependent diabetes mellitus and an increased risk of cardiovascular events. Abnormalities of blood coagulation (higher plasminogen activator inhibitor type I and fibrinogen levels), hyperuricemia and microalbuminuria have also been found in metabolic syndrome-X.

The instant inventors view the Syndrome X continuum in its cardiovascular light, while acknowledging its important metabolic component. The first stage of Syndrome X consists of insulin resistance, abnormal blood lipids (cholesterol and triglycerides), obesity, and high blood pressure (hypertension). Any one of these four first stage conditions signals the start of Syndrome X.

Each first stage Syndrome X condition risks leading to another. For example, increased insulin production is associated with high blood fat levels, high blood pressure, and obesity. Furthermore, the effects of the first stage conditions are additive; an increase in the number of conditions causes an increase in the risk of developing more serious diseases on the Syndrome X continuum.

A patient who begins the Syndrome X continuum risks spiraling into a maze of increasingly deadly diseases. The next stages of the Syndrome X continuum lead to overt diabetes, kidney failure, and heart failure, with the possibility of stroke and heart attack at any time. Syndrome X is a dangerous continuum, and preventative medicine is the best defense. Diseases are currently most easily diagnosed in their later stages, but controlling them at a late stage is extremely difficult. Disease prevention is much more effective at an earlier stage.

Subsequent to the isolation of particular disease state marker sequences as taught by the instant invention, the promulgation of various forms of risk-assessment tests are contemplated which will allow physicians to identify asymptomatic patients before they suffer an irreversible event such as diabetes, kidney failure, and heart failure, and enable effective disease management and preventative medicine. Additionally, the specific diagnostic tests which evolve from this methodology provide a tool for rapidly and accurately diagnosing acute Syndrome X events such as heart attack and stroke, and facilitate treatment. As an additional concept, the particular marker may be further validated by recognition of the corresponding autoantibody.

In order to purify the disease specific marker and further characterize the sequence thereof, additional processing was performed.

For example, Serum (20 ml) was (diluted 5-fold with phosphate buffered saline) concentrated by centrifugation through a YM3 MICROCON spin filter (Amicon) for 20 min at 10,000 RPM at 4°C in a Beckman MICROCENTRIFuge R model bench top centrifuge. The filtrate was discarded and the retained solution, which contained the two peptides of interest, was analyzed further by tandem mass spectrometry to deduce their amino acid sequences. Tandem mass spectrometry was performed at the University of Manitoba's (Winnipeg, Manitoba, Canada) mass spectrometry laboratory using the procedures that are well known to practitioners of the art.

In accordance with various stated objectives of the invention, the skilled artisan, in possession of the specifically isolated proteomic material, would readily carry out known techniques in order to raise purified biochemical materials, e.g. monoclonal and/or polyclonal antibodies, which are useful in the production of methods and devices useful as point-of-care rapid assay diagnostic or risk assessment devices as are known in the art.

The specific proteomic materials which are analyzed according to the method of the invention are released into the circulation and may be present in the blood or in any blood product, for example plasma, serum, cytolyzed blood, e.g. by treatment with hypotonic buffer or detergents and dilutions and preparations thereof, and other body fluids, e.g. CSF, saliva, urine, lymph, and the like. The presence of each proteomic material marker is determined using antibodies specific for each of the markers and

detecting specific binding of each antibody to its respective marker. Any suitable direct or indirect assay method may be used to determine the level of each of the specific markers measured according to the invention. The assays may be competitive assays, sandwich assays, and the label may be selected from the group of well-known labels such as radioimmunoassay, fluorescent or chemiluminescence immunoassay, or immunoPCR technology. Extensive discussion of the known immunoassay techniques is not required here since these are known to those of skilled in the art. See Takahashi et al. (Clin Chem 1999;45(8):1307) for S100B assay.

A monoclonal antibody specific against the proteomic material sequence isolated by the present invention may be produced, for example, by the polyethylene glycol (PEG) mediated cell fusion method, in a manner well-known in the art.

Traditionally, monoclonal antibodies have been made according to fundamental principles laid down by Kohler and Milstein. Mice are immunized with antigens, with or without, adjuvants. The splenocytes are harvested from the spleen for fusion with immortalized hybridoma partners. These are seeded into microtitre plates where they can secrete antibodies into the supernatant that is used for cell culture. To select from the hybridomas that have been plated for the ones that produce antibodies of interest the hybridoma supernatants are usually tested for antibody binding to antigens in an ELISA (enzyme linked immunosorbent assay) assay. The idea is that the wells that contain the hybridoma of interest will contain antibodies that will bind most avidly to the test antigen, usually the immunizing antigen. These wells are then subcloned in limiting dilution fashion to produce monoclonal hybridomas. The selection for the clones of interest is repeated using an ELISA assay to test for antibody binding. Therefore, the principle that has been propagated is that in the production of monoclonal antibodies the hybridomas that produce the most avidly binding antibodies are the ones that are selected from among all the hybridomas that were initially produced. That is to say, the preferred antibody is the one with highest affinity for the antigen of interest.

There have been many modifications of this procedure such as using whole cells for immunization. In this method, instead of using purified antigens, entire cells are used for immunization. Another modification is the use of cellular ELISA for screening. In this method instead of using purified antigens as the target in the ELISA,

fixed cells are used. In addition to ELISA tests, complement mediated cytotoxicity assays have also been used in the screening process. However, antibody-binding assays were used in conjunction with cytotoxicity tests. Thus, despite many modifications, the process of producing monoclonal antibodies relies on antibody binding to the test antigen as an endpoint.

The purified monoclonal antibody is utilized for immunochemical studies.

Polyclonal antibody production and purification utilizing one or more animal hosts in a manner well-known in the art can be performed by a skilled artisan.

Another objective of the present invention is to provide reagents for use in diagnostic assays for the detection of the particularly isolated proteomic materials of the present invention.

In one mode of this embodiment, the proteomic materials, e.g. the disease specific marker sequences of the present invention may be used as antigens in immunoassays for the detection of those individuals suffering from the disease known to be evidenced by said marker sequence. Such assays may include but are not limited to: radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), "sandwich" assays, precipitin reactions, gel diffusion immunodiffusion assay, agglutination assay, fluorescent immunoassays, protein A or G immunoassays and immunoelectrophoresis assays.

According to the present invention, monoclonal or polyclonal antibodies produced against the isolated proteomic materials of the instant invention are useful in an immunoassay on samples of blood or blood products such as serum, plasma or the like, spinal fluid or other body fluid, e.g. saliva, urine, lymph, and the like, to diagnose patients with the characteristic disease state linked to said marker sequence. The antibodies can be used in any type of immunoassay. This includes both the two-site sandwich assay and the single site immunoassay of the non-competitive type, as well as in traditional competitive binding assays.

Particularly preferred, for ease and simplicity of detection, and its quantitative nature, is the sandwich or double antibody assay of which a number of variations exist, all of which are contemplated by the present invention. For example, in a typical sandwich assay, unlabeled antibody is immobilized on a solid phase, e.g. microtiter

plate, and the sample to be tested is added. After a certain period of incubation to allow formation of an antibody-antigen complex, a second antibody, labeled with a reporter molecule capable of inducing a detectable signal, is added and incubation is continued to allow sufficient time for binding with the antigen at a different site, resulting with a formation of a complex of antibody-antigen-labeled antibody. The presence of the antigen is determined by observation of a signal which may be quantitated by comparison with control samples containing known amounts of antigen.

All patents and publications mentioned in this specification are indicative of the levels of those skilled in the art to which the invention pertains. All patents and publications are herein incorporated by reference to the same extent as if each individual publication was specifically and individually indicated to be incorporated by reference.

It is to be understood that while a certain form of the invention is illustrated, it is not to be limited to the specific form or arrangement herein described and shown. It will be apparent to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is shown and described in the specification and drawings/figures.

One skilled in the art will readily appreciate that the present invention is well adapted to carry out the objectives and obtain the ends and advantages mentioned, as well as those inherent therein. The oligonucleotides, peptides, polypeptides, biologically related compounds, methods, procedures and techniques described herein are presently representative of the preferred embodiments, are intended to be exemplary and are not intended as limitations on the scope. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention and are defined by the scope of the appended claims. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in the art are intended to be within the scope of the following claims.

APPENDIX A

Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
SJ CON 07	M	65	MI, Hx of arthritis,	MI	1020	Alpha Fibrinogen	(G)DFLAEGGGVR(G)
HNS-SJ28				MI	1020	Alpha Fibrinogen	(G)DFLAEGGGVR(G)
HNS-SJ33				MI	1020	Alpha Fibrinogen	(G)DFLAEGGGVR(G)
SJ CON 06	F	77		MI	1077	Alpha Fibrinogen	(E)GDFLAEGGGVR(G)
SJ CON 17	M	68	MI	MI	1077	Alpha Fibrinogen	(E)GDFLAEGGGVR(G)
SJ CON 19	M	62	Acute MI, SK???	MI	1077	Alpha Fibrinogen	(E)GDFLAEGGGVR(G)
SJ CON 21	M	65	Non-Q wave MI, Hx HTN	MI	1077	Alpha Fibrinogen	(E)GDFLAEGGGVR(G)
HNS-SJ28				MI	1077	Alpha Fibrinogen	(E)GDFLAEGGGVR(G)
SJ CON 05	F	67	Rectal bleed, Asthma, NIDDM	Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
SJ CON 06	F	77	MI, NIDDM.	Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
TWH-039	M	62	A.flb, Diabetes, smoker, HTN	Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
184-988	M	73		Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
TWH-039	M	62	A.flb, Diabetes, smoker, HTN	Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
184-988				Type II Diabetes	1097	Apolipoprotein	(D)PEVRPTSAVAA(-)
SJ CON 01	M	82		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 05	F	67		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 08	F	77		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 09	M	80		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 07	M	65		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 10	F	50		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 14	F	65		Renal Failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 04	M	66	Unstable angina, hemodialysis	Renal failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 11	M	68	Unstable angina, hemodialysis	Renal failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 13	F	80	Rapid atrial Fib. Prior Hx CAN hemodialysis	Renal failure	1206	Alpha Fibrinogen	(G)EGDFLAEGGGVR(G)
SJ CON 06	F	77		MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 07	M	65	GE (gastroesophageal) reflux	MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 10	F	60	Inferior MI, Hiatal Hernia	MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 14	F	65	MI, NIDDM	MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 17	M	68		MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 19	M	52		MI	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 21	M	65		MI	1211	Complement C3f	(H)RIHWESASLL(R)
HNS-SJ22				MI	1211	Complement C3f	(H)RIHWESASLL(R)
HNS-SJ28				MI	1211	Complement C3f	(H)RIHWESASLL(R)
HNS-SJ33				MI	1211	Complement C3f	(H)RIHWESASLL(R)
CU-15	F	54	Acute CVA, Basal ganglia	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used tPA	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-30	M	56	HTN, ICH	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1211	Complement C3f	(H)RIHWESASLL(R)

APPENDIX A

Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
23604 - KKB	M	61	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23707 - KL	F	65	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
20206 - MM	F	75	STAGE 4	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
20208 - HF	M	79	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23616 - JGK	M	43	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23421 - FB	M	59	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
22813 - CL	F	66	STAGE 4	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23106 - FC	M	64	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23116 - FC	M	59	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
23134 - FC	M	62	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1211	Complement C3f	(H)RIHWESASLL(R)
SJ CON 06	F	77		MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 07	M	65		MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 10	F	50	Hemodialysis	MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 14	F	65	hemodialysis	MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 17	M	58		MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 19	M	52		MI	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 21	M	65		MI	1348	Complement C3f	(T)HRIHWESASLL(R)
HNS-SJ22				MI	1348	Complement C3f	(T)HRIHWESASLL(R)
HNS-SJ28				MI	1348	Complement C3f	(T)HRIHWESASLL(R)
HNS-SJ33				MI	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-09	F	69	ICH, secondary to AVM	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-12	F	44	ICH	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-15	F	54	Acute CVA, Basal ganglia	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-10	M	66	HTN, ICH right thalmic	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used tPA	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-30	M	66	HTN, ICH	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)

APPENDIX A

Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
CU-60	M	64	HTN, Prior CVA, ICH (R thalamic hemorrhage)	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-66	M	49	HTN, Prior CVA, CVA	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
CU-75	M	43	HTN, Prior CVA, ICH	Stroke-ICH	1348	Complement C3f	(T)HRIHWESASLL(R)
23604 - KKB	M	61	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23707 - KL	F	65	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
20206 - MM	F	75	STAGE 4	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
20208 - HIF	M	79	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
22803 - HB	M	80	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23816 - JGK	M	43	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23421 - FB	M	59	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
22813 - CL	F	66	STAGE 4	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23116 - FC	M	59	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
23134 - FC	M	82	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1348	Complement C3f	(T)HRIHWESASLL(R)
SJ CON 01	M	82		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 05	F	67		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 06	F	77		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 08	F	77		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 09	M	80		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 07	M	65		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 07	M	65		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 10	F	60		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 10	F	60		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 14	F	65		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 14	F	65		Renal Failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 17	M	58		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 19	M	62		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 21	M	65		MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
HNS-SJ22				MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
HNS-SJ28				MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
HNS-SJ33				MI	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)

APPENDIX A

Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
SJ CON 04	M	66	Unstable angina, hemodialysis	Renal failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 11	M	68	Unstable angina, hemodialysis	Renal failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
SJ CON 13	F	80	Rapid atrial Fib, Prior Hx CAN hemodialysis	Renal failure	1350	Alpha Fibrinogen	(D)SESDFLAEGGGVR(G)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23421 - FB	M	69	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
22813 - CL	F	66	STAGE 4	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23130 - ER	M	61	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23105 - FC	M	64	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23116 - FC	M	59	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
20414 - EYG	F	76	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23130 - ER	M	61	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
23134 - FC	M	62	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
20102 - EAB	M	70	STAGE 3	CHF	1406	Serum Albumin	(R)DAHKSEVAHRFK(D)
SJ CON 06	F	77		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 07	M	66		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 10	F	60		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 14	F	65		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 17	M	58		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 19	M	52		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 21	M	65		MI	1449	Complement C3f	(I)THRIHWESASLL(R)
HNS-SJ22				MI	1449	Complement C3f	(I)THRIHWESASLL(R)
HNS-SJ28				MI	1449	Complement C3f	(I)THRIHWESASLL(R)
HNS-SJ33				MI	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-69	F	69	ICH, secondary to AVM	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-12	F	44	ICH	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-15	F	64	Acute CVA, Basal ganglia	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-10	M	66	HTN, ICH right thalmic	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-14	M	60	HTN, acute CVA	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-16	F	76	HTN, ICH (cerebellar vermis)	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used tPA	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-28	M	55	HTN, ICH	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-30	M	56	HTN, ICH	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-60	M	64	HTN, Prior CVA, ICH (R thalmic hemorrhage)	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-66	M	49	HTN, Prior CVA, CVA	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
CU-75	M	43	HTN, Prior CVA, ICH	Stroke-ICH	1449	Complement C3f	(I)THRIHWESASLL(R)
23604 - KKB	M	61	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23707 - KL	F	66	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
22703 - MMS	F	87	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
20206 - MM	F	75	STAGE 4	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
21813 - GR	F	85	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23008 - GFB	M	87	STAGE3 - DEAD	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
20208 - HIF	M	79	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23616 - JGK	M	43	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23421 - FB	M	69	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
22813 - CL	F	88	STAGE 4	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23116 - FC	M	69	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
23134 - FC	M	82	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1449	Complement C3f	(I)THRIHWESASLL(R)
SJ CON 01	M	82		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 05	F	67		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 06	F	77		Renal Failure	1466	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 09	M	80		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 07	M	65		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 10	F	60		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 14	F	65		Renal Failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 04	M	66	Unstable angina, hemodialysis	Renal failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 11	M	68	Unstable angina, hemodialysis	Renal failure	1466	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 13	F	80	Rapid atrial Fib, Prior Hx CAN hemodialysis	Renal failure	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
CU-12	F	44	ICH	Stroke-ICH	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
CU-10	M	68	HTN, ICH right thalmic	Stroke-ICH	1466	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
CU-16	F	76	HTN, ICH (cerebellar vermis)	Stroke-ICH	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1465	Alpha Fibrinogen	(A)DSGEGDFLAEGGGVR(G)
SJ CON 07	M	65		MI	1618	Alpha Fibrinogen	(T)ADSGEGDFLAEGGGVR(G)
SJ CON 10	F	50		MI	1618	Alpha Fibrinogen	(T)ADSGEGDFLAEGGGVR(G)
HNS-SJ22				MI	1618	Alpha Fibrinogen	(T)ADSGEGDFLAEGGGVR(G)
SJ CON 01	M	82		Renal Failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 05	F	67		Renal Failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 06	F	77		Renal Failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 09	M	80		Renal Failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
SJ CON 07	M	66		Renal Failure	1621	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 10	F	50		Renal Failure	1621	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 14	F	66		Renal Failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 04	M	66	Unstable angina, hemodialysis	Renal failure	1621	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 11	M	68	Unstable angina, hemosdialysis	Renal failure	1621	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 13	F	80	Rapid atrial Fib, Prior Hx CAN hemodialysis	Renal failure	1521	Serum Albumin	(R)DAHKSEVAHRFKD(L)
SJ CON 10	F	50		MI	1526	Serum Amyloid A	(D)PNHFRPAGLPEKY(-)
HNS-SJ22				MI	1626	Serum Amyloid A	(D)PNHFRPAGLPEKY(-)
HNS-SJ28				MI	1625	Serum Amyloid A	(D)PNHFRPAGLPEKY(-)
HNS-SJ22				MI	1536	Alpha Fibrinogen	(T)ADSGEGDFLAEGGGVR(G)
SJ CON 06	F	77		MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 07	M	65		MI	1562	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 10	F	60		MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 14	F	65		MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 17	M	68		MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 19	M	62		MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 21	M	66		MI	1562	Complement C3f	(K)ITHRIHWESASLL(R)
HNS-SJ22				MI	1562	Complement C3f	(K)ITHRIHWESASLL(R)
HNS-SJ33				MI	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23804 - KKB	M	61	STAGE 3	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23707 - KL	F	65	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
20206 - MM	F	76	STAGE 4	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
20208 - HIF	M	79	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23816 - JGK	M	43	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
20803 - EW	M	46	Acute MI - STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
23421 - FB	M	69	STAGE 3	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
22813 - CL	F	68	STAGE 4	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
23118 - FC	M	59	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1662	Complement C3f	(K)ITHRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
23134 - FC	M	62	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1562	Complement C3f	(K)ITHRIHWESASLL(R)
SJ CON 06	F	77		MI	1616	Complement C3f	

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
SJ CON 07	M	85		MI	1616	Complement C3f	
SJ CON 10	F	60		MI	1616	Complement C3f	
SJ CON 14	F	85		MI	1616	Complement C3f	
SJ CON 17	M	68		MI	1616	Complement C3f	
SJ CON 19	M	52		MI	1616	Complement C3f	
SJ CON 21	M	66		MI	1616	Complement C3f	
HNS-SJ22				MI	1616	Complement C3f	
HNS-SJ28				MI	1616	Complement C3f	
HNS-SJ33				MI	1616	Complement C3f	
SJ CON 06	F	77		MI	1690	Complement C3f	(S)KITHRIHWESASLL(R)
SJ CON 07	M	65		MI	1690	Complement C3f	(S)KITHRIHWESASLL(R)
SJ CON 10	F	50		MI	1690	Complement C3f	(S)KITHRIHWESASLL(R)
SJ CON 14	F	65		MI	1690	Complement C3f	(S)KITHRIHWESASLL(R)
SJ CON 17	M	58		MI	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-69	F	69	ICH, secondary to AVM	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-12	F	44	ICH	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-15	F	54	Acute CVA, Basal ganglia	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-10	M	66	HTN, ICH right thalmic	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-14	M	50	HTN, acute CVA	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-16	F	76	HTN, ICH (cerebellar vermis)	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used IPA	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-28	M	65	HTN, ICH	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-30	M	66	HTN, ICH	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-60	M	84	HTN, Prior CVA, ICH (R thalamic hemorrhage)	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-66	M	49	HTN, Prior CVA, CVA	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
CU-75	M	43	HTN, Prior CVA, ICH	Stroke-ICH	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23804 - KKB	M	61	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23707 - KL	F	65	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
20206 - MM	F	76	STAGE 4	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
20208 - HIF	M	78	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23816 - JGK	M	43	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23421 - FB	M	69	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
22813 - CL	F	68	STAGE 4	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23116 - FC	M	59	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23130 - ER	M	51	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
23134 - FC	M	62	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1690	Complement C3f	(S)KITHRIHWESASLL(R)
SJ CON 01	M	82	NIDDM, CHF, Hypothalamia??	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 01	M	82	patient died of CA Dec. 22/98	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 05	F	67	hemodialysis	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 06	F	77	hemodialysis	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 06	F	77		MI	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 09	M	80	NIDDM, HTN, Rlo?? Angina	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
TWH-002	M	81		Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
TWH -009	M	76	Aphasia, Rt hemiparalysis,	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 07	M	65		MI	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 10	F	50		MI	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 14	F	65		MI	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
SJ CON 17	M	66		MI	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-69	F	69	ICH, secondary to AVM	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-12	F	44	ICH	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-15	F	64	Acute CVA, Basal ganglia	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-10	M	66	HTN, ICH right thalmic	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-14	M	50	HTN, acute CVA	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-16	F	76	HTN, ICH (cerebellar vermis)	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used tPA	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-28	M	55	HTN, ICH	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-30	M	56	HTN, ICH	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-60	M	84	HTN, Prior CVA, ICH (R thalamic hemorrhage)	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-66	M	49	HTN, Prior CVA, CVA	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
CU-75	M	43	HTN, Prior CVA, ICH	Stroke-ICH	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23804 - KKB	M	61	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23707 - KL	F	65	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
20208 - MM	F	75	STAGE 4	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
20208 - HIF	M	79	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23616 - JGK	M	43	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
2c803 - EW	M	45	Acute MI - STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23421 - FB	M	69	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
22813 - CL	F	68	STAGE 4	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23116 - FC	M	69	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
20414 - EYG	F	78	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
23134 - FC	M	62	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
20102 - EAB	M	70	STAGE 3	CHF	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
TWH-002	M	81		Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
TWH -009	M	76	Aphasia, Rt hemiparalysis,	Type II Diabetes	1777	Complement C3f	(S)SKITHRIHWESASLL(R)
TWH-002				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
TWH -009				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
TWH-024				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
TWH-039				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
743-450				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
184-988				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
734-989				Type II Diabetes	1845	Complement C4 fragment	(+)RNGFKSHALQLNNRQIR(-)
SJ CON 01	M	82		Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 08	F	77		Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 06	F	77		MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 09	M	80	Hx of prostate CA, hemodialysis	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-002	M	81		Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH -009	M	76	Complete hemianopia, smoker	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-024	M	63	Stroke, PM Hx, NIDDM, Incr BP	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-039	M	62		Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
184-988	M	73	NIDDM	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
734-989	M	65	NIDDM	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 07	M	65		MI	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 10	F	60		MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 14	F	65		MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 17	M	68		MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
SJ CON 19	M	62		MI	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 21	M	65		MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
HNS-SJ22				MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
HNS-SJ28				MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
HNS-SJ33				MI	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-69	F	69	ICH, secondary to AVM	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-12	F	44	ICH	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-15	F	64	Acute CVA, Basal ganglia	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-10	M	66	HTN, ICH right thalmic	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-14	M	50	HTN, acute CVA	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-16	F	76	HTN, ICH (cerebellar vermis)	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-18	M	72	HTN, previous CVA, CVA (R MCA) used tPA	Stroke-ICH	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-19	M	47	CVA, transfer to VA	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-28	M	65	HTN, ICH	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-30	M	66	HTN, ICH	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-33	M	72	Prior CVA, acute CVA (L MCA)	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-37	M	72	HTN, acute CVA (R subcortical	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-38	F	67	HTN, Diabetes, acute CVA (R parietal)	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-60	M	64	HTN, Prior CVA, ICH (R thalamic hemorrhage)	Stroke-ICH	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-66	M	49	HTN, Prior CVA, CVA	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
CU-75	M	43	HTN, Prior CVA, ICH	Stroke-ICH	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23504 - KKB	M	61	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23707 - KL	F	85	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
22703 - MMS	F	67	STAGE 3	CHF	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
20206 - MM	F	75	STAGE 4	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
22103 - GM	F	77	STAGE 3	CHF	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
21813 - GR	F	65	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23402 - HM	M	67	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
20208 - HIF	M	78	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
22803 - HB	M	60	STAGE 3	CHF	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
23616 - JGK	M	43	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23421 - FB	M	59	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
22813 - CL	F	66	STAGE 4	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1866	Complement C3f	(+)SSKITHRIHWESASLL(R)
23105 - FC	M	64	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23116 - FC	M	69	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
20414 - EYG	F	76	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23130 - ER	M	61	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
23134 - FC	M	62	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
20102 - EAB	M	70	STAGE 3	CHF	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-002				Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH -009			Complete hemianopia, smoker	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-024	M	63	Stroke, PM Hx, NIDDM, Incr BP	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
TWH-039				Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
184-888	M	73	NIDDM	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
734-889	M	65	NIDDM	Type II Diabetes	1865	Complement C3f	(+)SSKITHRIHWESASLL(R)
SJ CON 07	M	65		MI	1896	Complement C4A	(R)NGFKSHALQLNNRQIR(G)
SJ CON 17	M	58		MI	1896	Complement C4A	(R)NGFKSHALQLNNRQIR(G)
HNS-SJ22				MI	1896	Complement C4A	(R)NGFKSHALQLNNRQIR(G)
TWH-002				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
TWH -009				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
TWH-024				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
TWH-039				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
743-450				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
184-888				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
734-889				Type II Diabetes	1998	Complement C3f	(+)SSKITHRIHWESASLL(-)
SJ CON 01	M	82		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(+)
SJ CON 06	F	77		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(+)
SJ CON 06	F	77		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 09	M	80		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(+)
TWH-002	M	81		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH -009	M	78		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(+)
TWH-024	M	63		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH-039	M	62		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(+)
184-888	M	73		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
734-889	M	65		Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 07	M	65		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 10	F	50		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 14	F	65		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 17	M	58		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 19	M	62		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
SJ CON 21	M	65		MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
HNS-SJ22				MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
HNS-SJ28				MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
HNS-SJ33				MI	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23604 - KKB	M	61	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23707 - KL	F	65	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
22703 - MMS	F	67	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
20206 - MM	F	75	STAGE 4	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
22103 - GM	F	77	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
21813 - GR	F	65	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23008 - GFB	M	67	STAGE3 - DEAD	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23402 - HM	M	67	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
20208 - HIF	M	79	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
22803 - HB	M	60	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23616 - JGK	M	43	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
20803 - EW	M	45	Acute MI - STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23421 - FB	M	59	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
22813 - CL	F	66	STAGE 4	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23130 - ER	M	51	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23105 - FC	M	64	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23116 - FC	M	69	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
20414 - EYG	F	78	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23130 - ER	M	51	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23134 - FC	M	62	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
20102 - EAB	M	70	STAGE 3	CHF	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH-002				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH -009				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH-024				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
TWH-039				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
184-988				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
734-989				Type II Diabetes	2021	Complement C3f	(+)SSKITHRIHWESASLLR(-)
23604 - KKB	M	61	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23707 - KL	F	65	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
22703 - MMS	F	67	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
20206 - MM	F	75	STAGE 4	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
22103 - GM	F	77	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
21813 - GR	F	65	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23008 - GFB	M	67	STAGE3 - DEAD	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23402 - HM	M	67	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
20208 - HIF	M	79	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
22803 - HB	M	60	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23616 - JGK	M	43	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
20803 - EW	M	45	Acute MI - STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23421 - FB	M	59	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
22813 - CL	F	66	STAGE 4	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23130 - ER	M	51	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23105 - FC	M	64	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23116 - FC	M	69	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
20414 - EYG	F	78	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
23130 - ER	M	51	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR

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Code #	Gender	Age	Patient History	Disease	MW	Protein Name	Sequence
23134 - FC	M	62	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
20102 - EAB	M	70	STAGE 3	CHF	2056	Complement C3f	SSKITHRIHWESASLLR
3111898	M	?	Insulin Resistance	Insulin Resistance	2267	Apolipprotein E	(A)TVGSLAGQPLQERAQAWGERL(R)
112698	F	?	Insulin Resistance	Insulin Resistance	2267	Apolipprotein E	(A)TVGSLAGQPLQERAQAWGERL(R)
6124698	F	?	Insulin Resistance	Insulin Resistance	2267	Apolipprotein E	(A)TVGSLAGQPLQERAQAWGERL(R)
3111898	M	?	Insulin Resistance	Insulin Resistance	2763	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLI)
42698	M	?	Insulin Resistance	Insulin Resistance	2763	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLI)
112698	F	?	Insulin Resistance	Insulin Resistance	2763	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLI)
6101600	F	?	Insulin Resistance	Insulin Resistance	2763	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLI)
5124698	F	?	Insulin Resistance	Insulin Resistance	2763	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLI)
3111898	M	?	Insulin Resistance	Insulin Resistance	2937	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLIA(F)
42698	M	?	Insulin Resistance	Insulin Resistance	2937	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLIA(F)
112698	F	?	Insulin Resistance	Insulin Resistance	2937	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLIA(F)
6101600	F	?	Insulin Resistance	Insulin Resistance	2937	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLIA(F)
5124698	F	?	Insulin Resistance	Insulin Resistance	2937	Serum Albumin	(R)DAHKSEVAHRFKDLGEENFKALVLIA(F)

CLAIMS

What is claimed is:

Claim 1. A process for determining a proteomic basis for development and progression of abnormal physiological conditions comprising:

obtaining a patient sample containing proteomic material;

preparing said patient sample to facilitate proteomic investigation thereof;

isolating one or more patient specific proteomic materials from said patient sample; and

comparing said one or more isolated patient specific proteomic materials against a library of proteomic materials having characteristics identifiable with both normal and abnormal physiological conditions or predictive hallmarks thereof;

wherein said one or more isolated patient specific proteomic materials are characterized as being positively or negatively indicative of one or more abnormal physiological conditions or predictive hallmarks thereof.

Claim 2. A process in accordance with claim 1, further including the step of:

sequencing said one or more isolated patient specific proteomic materials.

Claim 3. A process in accordance with claim 1, further including the step of:

developing at least one antibody to said isolated patient specific proteomic material.

Claim 4. A process in accordance with claim 3, further including the step of:

expressing at least one protein marker specific to said at least one antibody to said isolated patient specific proteomic material.

Claim 5. A process in accordance with claim 3, further including the step of:

performing at least one interactive mapping step to characterize said at least one antibody.

Claim 6. A process in accordance with claim 5 wherein said interactive mapping step includes one or more steps selected from the group consisting of creation of engineered antibodies, directly determining the three-dimensional structure of said antibody directly from an amino acid sequence thereof; cellular localization, sub-cellular localization, protein-protein interaction, receptor-ligand interaction, and pathway delineation.

Claim 7. A process in accordance with claim 6 wherein said engineered antibodies are antibodies tagged with a material selected from the group consisting of GFP, colloidal gold, streptavidin, avidin and biotin.

Claim 8. A process in accordance with claim 4, further including the step of:

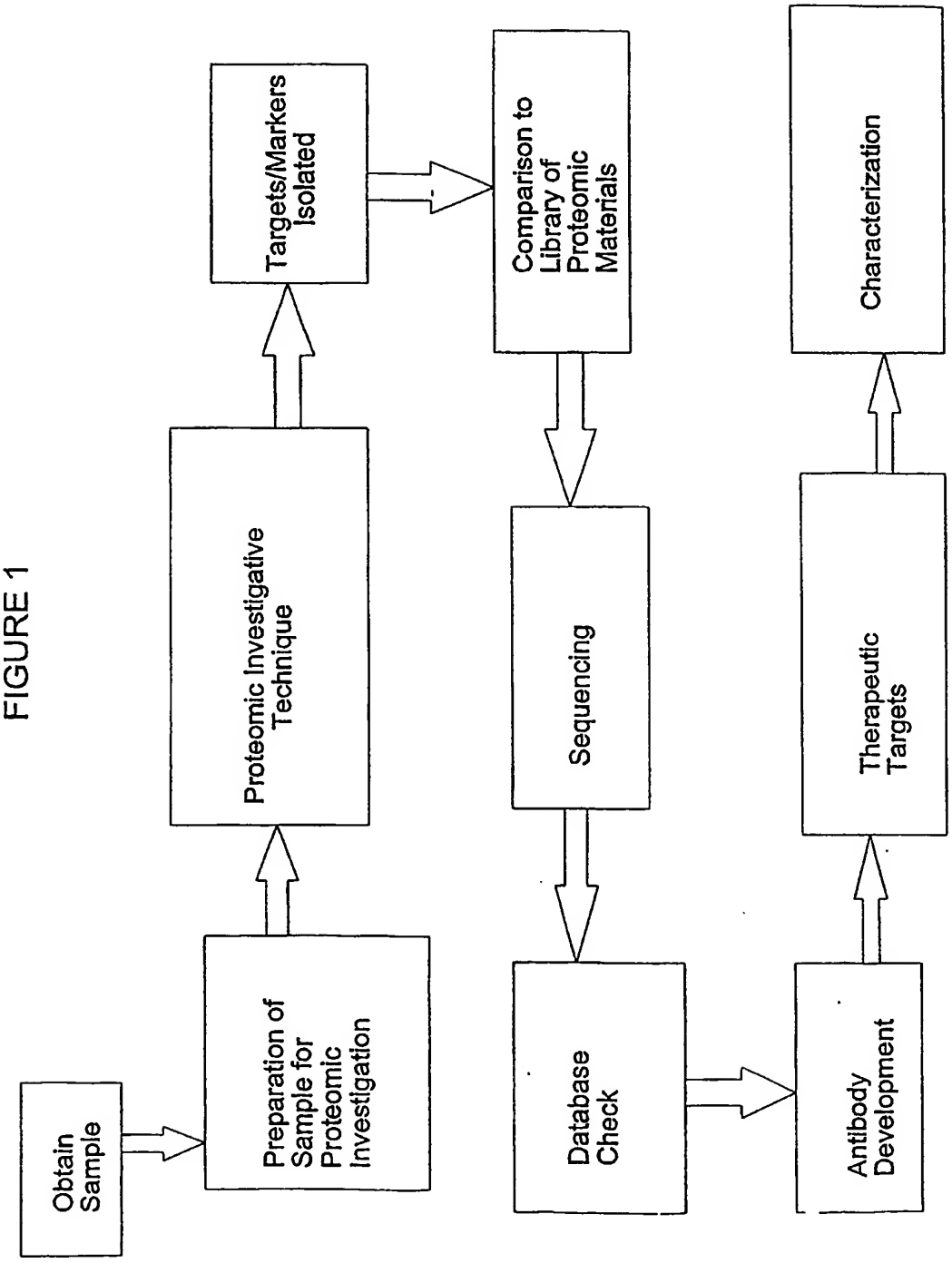
performing at least one interactive mapping step to characterize said at least one protein marker.

Claim 9. A process in accordance with claim 8 wherein said interactive mapping step includes one or more steps selected from the group consisting of creation of engineered proteins, directly determining the three-dimensional structure of said

protein directly from an amino acid sequence thereof; cellular localization, sub-cellular localization, protein-protein interaction, receptor-ligand interaction, and pathway delineation.

Claim 10. A process in accordance with claim 9 wherein said engineered proteins are proteins tagged with a material selected from the group consisting of GFP, colloidal gold, streptavidin, avidin and biotin.

FIGURE 1


Obtain Sample
Preparation of Sample for Proteomic Investigation
Proteomic Investigative Technique
Targets/Markers Isolated
Comparison to Library of Proteomic Materials
Sequencing
Database Check
Antibody Development
Therapeutic Targets
Characterization